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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/815,944	03/22/2001	Keith D. Allen	R-654	8251

7590 04/28/2005

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EXAMINER	
QIAN, CELINE X	

ART UNIT	PAPER NUMBER
1636	

DATE MAILED: 04/28/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/815,944	ALLEN ET AL.	
	Examiner	Art Unit	
	Celine X. Qian Ph.D.	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 April 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *30 and 32-39* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *30 and 32-39* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *22 March 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims 30 and 32-39 are pending in the application.

This Office Action is in response to the Amendment filed on 4/13/05.

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 4/13/05 has been entered.

Response to Amendment

Claims 30, 32-39 are rejected under 35 U.S.C.101/112 1st paragraph for reasons set forth in the previous office actions and discussed below.

Claims 30, 32-39 are rejected under 35 U.S.C. 112 2nd paragraph for reasons discussed below.

Response to Arguments

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 30, 32-39 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a credible, substantial and specific asserted utility or a well established utility.

Claims 30, 32-39 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a credible, substantial and specific asserted utility or a well established utility.

The claims are drawn to a transgenic mouse whose genome comprises a null endogenous melanocyte stimulating hormone receptor allele, wherein the null allele comprises polynucleotide sequence encoding a selection marker, wherein the mouse is homozygous for said null allele, the transgenic mouse exhibits, relative to a wild type mouse, hypoactivity demonstrated by increased total distance traveled in the open field test. The claims are further drawn to a cell or tissue isolated from said mouse and a method for producing said mouse.

No well-established utility exists for the claimed transgenic mouse. However, the specification asserts or implies the following as credible, specific and substantial patentable utilities for the claimed transgenic knockout mouse and cells or tissues isolated from said mouse:

1) To be used in methods of identifying agents capable of affecting a phenotype of said mouse.

2) To identify agents useful as therapeutic agents for treating conditions associated with a disruption or other mutation of the melanocyte stimulating hormone receptor gene.

3) To identify agents having an effect on melanocyte stimulating hormone receptor expression or function.

4) To serve as models for diseases.

5) To test and develop new treatments relating to the behavioral phenotypes.

Each of the following shall be addressed in turn:

1) To be used in methods of identifying agents capable of affecting a phenotype of said mouse. This utility is not credible, substantial and specific because the specification does not disclose a utility for such agents. The phenotype of hypoactivity demonstrated by increased total distance traveled in the open field test is resulted from the disruption of a single gene melanocyte stimulating hormone receptor, however, such genotypic-phenotypic association is not known in the art for relating to a specific disease. Although the agents can affect a phenotype in said transgenic mouse or a cell/tissue isolated from said mouse, the utility is not substantial because there is no other use of said agents except affecting a phenotype only exists in a mouse model. Since this asserted utility is not presented in mature form so it could be readily used in a real world sense, the asserted utility is not credible, substantial and specific.

2) To identify agents useful as therapeutic agents for treating conditions associated with a disruption or other mutation of the melanocyte stimulating hormone receptor gene. This utility is not credible, specific and substantial because the specification does not disclose what kind of conditions is associated with a disruption or other mutations of the melanocyte stimulating hormone receptor gene. The specification also fails to teach what specific condition is associated with the hypoactivity. The art teaches that no single behavior measured in the open field appears to reflect only anxiety or emotional reactivity (see Crawley et al. 1997). The art does not recognize any disorder having hypoactivity that is result from disruption of melanocyte stimulating hormone receptor gene. As such, the claimed mouse is not a valid model for any disorder. Since

this asserted utility is not presented in mature form so it could be readily used in a real world sense, the asserted utility is not credible, specific and substantial.

3) To identify agents having an effect on melanocyte stimulating hormone receptor expression or function. This asserted utility is not credible, substantial and specific because the specification does not disclose 1) how to use a mouse or cell that does not express melanocyte stimulating hormone receptor to identify agents which affect the gene expression or function; 2) how to use such identified agents that affect melanocyte stimulating hormone receptor expression or function. Since the identified agents does not have a substantial utility, the claimed mouse or mouse cells used in a method for identifying such agents does not have substantial utility as well. This asserted utility is not credible since there is no expression or function can be monitored in the knockout mouse or cells/tissues isolated from said mouse, it is unclear how these agents that affect melanocyte stimulating hormone receptor expression/function can be identified.

4) To serve as models for diseases. The asserted utility is not credible, substantial and specific because the specification does not disclose what types of disease the transgenic mouse or cells/tissues isolated from said mouse represents (see discussion in 2).

5) To test and develop new treatments relating to the behavioral phenotypes. This utility is not credible, substantial and specific because the specification does not teach what type of behavioral disorder the claimed mouse represents. As discussed above, the art does not recognize the claimed mouse as a valid behavioral model for any disorder. As such, it is not a valid model for any behavioral disorder. Since this asserted utility is

not presented in mature form so it could be readily used in a real world sense, the asserted utility is not credible, specific or substantial.

Since the claimed transgenic mouse and cells/tissues isolated from said mouse does not have utility, the method for producing said transgenic mouse does not have utility either. Therefore, the claimed invention lacks patentable utility for reasons given above.

Claims 30, 32-39 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a credible, substantial and specific asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention. (see also the reasons set forth in the office action mailed on 6/3/04 and 1/13/05).

The following is answers to Applicant's argument.

In response to the 112 1st rejection, Applicant asserts that the claims are drawn to a transgenic mouse having a disrupted melanocyte stimulating hormone receptor gene and a transgenic mouse whose genome comprises a null allele which comprises polynucleotide encoding a selection marker. Applicant argues that the claimed invention has patentable utility according to utility guidelines set forth in MPEP because the claimed invention has a well-established utility. Applicant assert that the skilled in the art would immediately appreciate how to use a knockout mouse because any knockout mouse has the inherent and well-established utility of defining the function and role of the disrupted gene regardless of specific phenotypes, characterizations or properties of the knockout mouse. Applicant further cites a passage at NIH website which indicate

that knockout mice represent a critical tool in studying gene function. Furthermore, Applicant asserts that the newly amended claims drawn to transgenic mouse comprising null-reporter alleles "is an indispensable starting point for studying the function of every gene"(Austin et al., 2004), "is an invaluable tool for investigating gene function on a genomic scale"(Molecular biology of Cell, Albert, 4th ed., Garland Science (2002), "is a powerful tool to investigate directly the importance and function of the gene" (Genes VII, Oxford university 2000), "offers a powerful approach to study gene function in a mammalian organism," (Joyner, Gene targeting: A Practical Approach, Oxford University Press 2000), "has revolutionized our ability to study gene function in cell culture *in vivo*," (Matise, Production of Targeted Embryonic Stem Cell Clones), and "provide an important means for understanding gene function."(Crawley, what's wrong with my mouse behavioral phenotype of transgenic and knockout mice, Wiley-Liss 2000). Moreover, Applicants indicates (and also by Declaration from Driscoll) that the claimed invention is purchased by two large pharmaceutical company and database comprising tests of the mouse has been subscribed by three pharmaceutical companies, thus such commercial acceptance more than satisfied the practical utility requirement of 101 and 112 1st paragraph according to *Brenner v. Manson* and *Phillips Petroleum Co. v. U.S. Steel Corp.*, and Lipscomb's Walker on Patents 5:17, p 562 (utility may be evidenced by sales and commercial demand). Moreover, Applicant asserts that the knockout mouse have a clear, specific and unquestionable utility as with gas chromatographs, screening assays and nucleotide sequence techniques as taught by MPEP 2107.01,I. Furthermore, Applicant also asserts that the claimed invention is useful for a particular purpose since the mouse has specific disclosed phenotype. Applicant

argues that the utility of the claimed inventions does not depend on a correlation between the disclosed phenotype and a disease in human according to *In re Brana*, in which the court decided that the applicants should not have been required to substantiate their presumptively correct disclosure to avoid a 112 1st rejection because the PTO had not satisfy the initial burden of providing evidence to doubt the asserted utility. Applicant asserts that similar to *Brana*, Applicant has asserted that the claimed invention is useful for a particular purpose, and such assertion would be considered credible by a person of ordinary skill in the art. Applicant argues that since the claimed knockout mouse has specific phenotypes, it is recognized in the art as a widely accepted model for determine gene function, both in mouse and humans (Austin and Doetschman). Applicant asserts that the Federal court found that utility had been demonstrated because the claimed compound had activity against a murine tumor implanted in a mouse in *Brana*, which is similar to the instant case in which the knockout mouse with a specific gene disrupted is a widely accepted model. Applicant argues that definitive proof that the phenotype observed in the null mouse would be the same as those in human is not a prerequisite to satisfying the utility requirement. Furthermore, Applicant argues that the present invention requires no further research to establish any utility because the specification has disclosed the melanocyte stimulating hormone receptor gene is associated with a condition, such as hypoactivity, which has immediate benefit to the public. Applicant asserts that use of the mouse to study gene function is credible and specific. Applicant argues that the examiner has not set forth any reason to doubt the objective truth of the statements made in the specification, particularly with respect to the claimed transgenic mouse. Lastly, Applicant argues that it is well known that melanocyte stimulating

hormone receptor are involved in the autocrine regulation of inflammation, thus the claimed mouse is useful to study the inflammatory process in macrophages mediated by nitric oxide, neopterin, and/or TNF-α. Applicant asserts that the claimed mouse can represent a disease model such as Wegener's Granulomatosis. Applicant thus concludes that the claimed invention has credible, substantial and specific utility which satisfies the statue of 35 U.S.C. 101, and enabled by the instant specification.

These arguments have been fully considered but deemed unpersuasive. The reasons for the utility and non-enablement rejection were discussed in detail in the office action mailed on 1/13/05 and in the utility rejection discussed above. In response to Applicant's response regarding any knockout mouse has a well-established utility, the examiner does not agree with Applicant's assertion that the claimed invention has a well-established utility. Applicant is reminded that in MPEP, the guideline for the utility requirement clearly states: "An invention has a well-established utility if (i) a person of ordinary skill in the art would immediately appreciate why the invention is useful based on the characteristics of the invention (e.g., properties or applications of a product or process), and (ii) the utility is specific, substantial, and credible." In the instant case, the utility that applies to any knockout mouse is not specific to the claimed invention, the melanocyte stimulating hormone receptor transgenic mouse having a null allele that comprises exogenous DNA. It was well known to knock out a gene to determine its function or what will happen when the gene is not expressed. However, scientific "utility" is not the same as "patentable utility" or a "well-established" utility, of which must be specific, substantial and credible. At the

time of filing, knockout mice were used for further research in the art as indicated by the quotations cited by Applicant, for example, studying gene function. However, further research does not rise to the level of a "well-established utility" because such a utility is not substantial. The utility guidelines specifically state that further research is not a "substantial utility." The MPEP states "the following are examples of situations that require or constitute carrying out further research to identify or reasonably confirm a "real world" context of use and, therefore, do not define "substantial utilities": A. Basic research such as studying the properties of the claimed product itself or the mechanisms in which the material is involved..." In the instant case, further study of mice would have been required to determine how to use the mouse of applicant's invention according to the embodiments described in the specification since the overall phenotype of the claimed mice does not correlate with any disorder; Therefore, further study would be required to determine how to use the mice to study a disorder, screening drugs and treatment for such disorder (the asserted utility in the specification). With regard to the well-established utility of studying gene function as asserted by Applicant, Olsen (GABA in the Nervous System, 2000, pg 81-95) taught that "although gene targeting is often useful in delineating the contribution of a given gene product to phenotypic characteristics observed, some gene knockouts lead to embryonic or perinatal lethality, and others lead to no apparent phenotype. This can arise from a lack of any role for the gene in question in regard to the trait studies or from compensation by other gene products. Analysis of the compensation can yield valuable clues to the genetic

pathway" (pg 82, last 11 lines of col. 1). As such, a knockout mice may not be capable of elucidating the function of the protein and may only provide a clue to a pathway the protein being knocked out is involved in. Using the claimed mice to obtain a clue to a pathway is not a "substantial utility." Using a mouse with a phenotype caused by genes compensating for a knocked out gene is not a "specific utility" because the phenotype is not specific to the knocked out gene.

In response to Applicant's argument of the commercial sale of the claimed mouse, Applicant is reminded that the sale of a product does not automatically gives the product patentable use according to the statue of 35 U.S.C.101 and the utility guideline set forth in the MPEP. Commercial success is only considered as secondary evidence for overcoming a 103 (a) rejection according to guidelines set by MPEP. *Brenner v. Manson* does not validate the notion that commercial use automatically gives a claimed product patentable utility. The subscription of three company to the Deltabase does not give automatically gives the claimed mouse patentable utility because it is unclear what data the companies are interested and what they are used for. The declaration under 37 CFR 1.132 has been fully considered, however, it is not sufficient to provide a patentable utility and enable the instantly claimed invention. The purchase of the claimed mouse by two large pharmaceutical company neither proves commercial success of the claimed mouse nor does it gives the claimed mouse a patentable utility. The case law of *Phillips Petroleum Co. v. U.S. Steel Corp.* 6 USPQ 2d 1065 talks about commercial success in context as secondary consideration in favor of nonobviousness (see page 1096). It states "of course, there must be a nexus "between the merits of the claimed invention and the evidence offered if that evidence is to be given substantial weight enroute to conclusion

on the obviousness issue." *Stratoflex* , 713 F.2d at 1539 [218 USPQ at 879] (noting *Solder Removal Co. v. United States Intern. Trade* , 582 F.2d 628, 637 [199 USPQ 129, 137] (C.C.P.A. 1978)). Crystalline polypropylene is one of the most widely used chemical compositions in commerce today. Worldwide demand is presently approximately fourteen billion pounds, with the United States' demand totaling nearly six billion pounds per year. (Mark, Tr. at 503.) 68 Experts from both sides were in general agreement that crystallinity is the characteristic which gives polypropylene its immense commercial value." According to the case law, the commercial success is established by the worldwide use of the claimed compositions and the generation of high revenue from the sale of the claimed composition. However, the sale of the present claimed invention to two pharmaceutical company clear does not mount to such "commercial success." The case law of 9 USPQ 2d 1461 affirmed the earlier case but does not deal with commercial success and practical utility. It states: "correct finding of infringement of otherwise valid claims mandates as a matter of law a finding of utility under §101," however, it does not apply to the current situation since there is no infringement of the current claimed invention. Furthermore, it is unclear how the claimed invention is going to be used by this pharmaceutical company. For instance, if the company is using the mouse for studying the function of the melanocyte stimulating hormone receptor gene, it at most gives the claimed mouse a scientific utility, which is different from the patentable utility for reasons discussed above. With regard to the sentence quoted from Lipscomb's Walker on Patents, the examiner cannot comment on it because it is unclear what context such statement was made. For example, what evidence should Applicants provide to establish sales and commercial demand? Is it a secondary evidence to some other

requirement? A search of the book reveals that it ends at page 530, there is no page or paragraph 562. As such, this statement alone does not support that sale of this mouse to one company automatically gives the claimed mouse a patentable utility. Therefore, based on the utility requirement set forth in MPEP, the sale of the mouse to one company does not give the claimed mouse a patentable utility.

In response to Applicant's argument regard *In re Brana*, the examiner does not agree that this case law applies to the instant case. In the *Brana* decision, the court concluded that the mouse tumor models (leukemia cell lines were originally derived from lymphocytic leukemia in mice) represent a specific disease against which the claimed compounds were alleged to be effective. As such, the claimed compound has credible, substantial and specific utility. In *Brana*, the asserted utility meets the requirement of the statue because the claimed compounds are effective in a valid and specific mouse tumor model. However, in the instance case, the claimed knockout mouse does not have a credible, substantial and specific use because the specification does not teach what specific disease model the claimed mouse represents and/or what type of drug the claimed mouse can screen. Although Applicant asserts that the claimed mouse is a widely accepted model, the prior art is in fact silent on the claimed mouse thus does not recognize any well-established utility for the claimed mouse. The examiner is not asking for definitive proof that the phenotype of the null mouse is same as those in human, but some credible teaching from the specification about what type of model the claimed mouse represents. Moreover, the utility of using the claimed mouse to study melanocyte stimulating hormone

receptor function or association to the phenotype is not a credible, substantial and specific utility for reasons discussed above. Furthermore, it is unclear whether all the phenotypes recited are result directly from the disruption of the melanocyte stimulating hormone receptor, secondary to said disruption or compensatory effect from other genes. Clearly, further research is required to determine the function of the melanocyte stimulating hormone receptor gene, thus said mouse lack substantial utility. Therefore, unlike *Brana,* the instant specification fails to provide a credible, substantial and specific utility for the claimed mouse. Lastly, Applicant's assertion that the claimed mouse may serve as a model for chronic inflammatory disease is not credible because the disclosed phenotype of the mouse is hypoactivity. It is unclear how a mouse with such phenotype can be used for a model of inflammatory disease. The nexus between the phenotype and the alleged disease model is apparently missing.

For reasons given in the previous office action and above, the specification fails to disclose a credible, substantial and specific use for the claimed mouse and one skilled in the art would not know how to use the claimed mouse according to the embodiments disclosed by the instant specification. The claims are thus rejected under 101/112 1st paragraph.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 30, 32-39 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Regarding claims 30, 32-39, the recitation of "mRNA comprising a polynucleotide sequence of SEQ ID NO:19" renders the claim indefinite because SEQ ID NO:19 is a DNA sequence rather than an RNA sequence. Further, the recitation of "wherein said endogenous allele encodes mRNA ...SEQ ID NO:19" also renders the claim indefinite because it is unclear whether the allele refers to the wild type or null allele.

Regarding claim 30, the recitation of "pseudopregnant mouse gives birth" renders the claim indefinite because a "pseudopregnant mouse" cannot give birth.

Please note, claim 39 recites "travele" on line 1, this is not a word. If it is a typographical error, please make appropriate correction.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Celine X. Qian Ph.D. whose telephone number is 571-272-0777. The examiner can normally be reached on 9:30-6:00 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel Ph.D. can be reached on 571-272-0781. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Celine X Qian Ph.D.
Examiner
Art Unit 1636

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PATENT EXAMINER